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Epidemiology Review of Study on Acetaminophen Use in Pregnancy and Risks of ADHD in Offspring

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EXECUTIVE SUMMARY

This review provides for the Division of Nonprescription Regulation Development (DNRD) a summary and critique of a study recently published in *JAMA Pediatrics* that reported an increased association between acetaminophen (APAP) use in pregnancy and attention deficit/hyperactivity disorder (ADHD) in the offspring.

APAP is the most widely-used over-the-counter analgesic and anti-pyretic in the U.S. Data from U.S. pregnancy databases indicate 65-70% of pregnant U.S. women report using APAP anytime during pregnancy[1]. Despite frequent use, little data exists on its safety during pregnancy. A recent issue of *JAMA Pediatrics* featured a study by Liew et al[2] that reported increased associations between prenatal APAP exposure and ADHD. On March 12 2014, the members of DNRD, Division of Epidemiology-I (DEPI-I), Pediatric and Maternal Health Staff (PMHS), and Office of Communications met to discuss the agency's response to the published study. DEPI agreed to provide a summary and critique of the study by Liew et al[2].

Liew et al[2] conducted a prospective cohort study using data from the Danish National Birth Cohort, maternal interview data, and Danish administrative health care data. The authors interviewed pregnant women twice during pregnancy and once after pregnancy for APAP use and medical history. Assessed outcomes included ADHD-like behaviors based on maternal interview of the child's behaviors at age 5, HKD diagnosis and ADHD medication use beginning at age 7.

Mothers reporting any APAP use during pregnancy reported more ADHD-like behavior in the offspring compared to unexposed mothers (aRR=1.13, 95% CI=1.01-1.27). Women reporting any APAP use in pregnancy were also significantly more likely to have a child with an HKD diagnosis (aRR=1.37, 95% CI=1.19-1.59) or a child who used ADHD medications (aHR=1.29, 95% CI=1.15-1.44), compared to unexposed women. Associations for all outcomes were strongest for APAP use in multiple trimesters and for more than 20 weeks in pregnancy. Findings from two other studies not assessing ADHD are conflicting: one study reported no associations between prenatal APAP and low IQ and attention decrements in the offspring[3], while another study reported significant associations between APAP use in pregnancy and externalizing behaviors and higher activity levels[4].

Based on the study findings, we note the following:

- *Results from Liew et al[2] demonstrate a consistent positive association between reported APAP use in pregnancy and risk of ADHD-related outcomes in the offspring.*
- *Residual and unmeasured confounding might explain the observed increased associations.*
- *The absence of information on APAP strength and number of pills taken precludes any meaningful interpretation of a dose-response relationship.*
- *The prospective study design and exposure ascertainment via maternal interview reduces the potential for selection bias and information bias, respectively.*
- *The authors did not assess clinical ADHD diagnoses; however their use of multiple study endpoints from different data sources likely captured a wide range of ADHD severity.*
- *Findings from two additional studies are of unknown clinical significance, but results from one of these studies might strengthen the evidence for an association between prenatal APAP exposure and ADHD risk.*

Positive associations observed between prenatal APAP exposure and ADHD in the offspring as reported by Liew et al[2] are noteworthy especially given the frequent use of APAP during

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pregnancy. However, the study's findings are difficult to interpret due to methodologic limitations and in the context of other existing evidence.

We recommend no regulatory action be taken at this time based on available data. Given the observed safety signal, we recommend DEPI and DNRD stay current on the published safety literature related to APAP use in pregnancy. We further recommend the addition of this safety signal to ongoing agency discussions regarding the safety and regulation of analgesic use during pregnancy.

1 INTRODUCTION

This purpose of this review is to provide for the Division of Nonprescription Regulation Development (DNRD) a summary and critique of a study recently published in *JAMA Pediatrics* that reported an increased association between acetaminophen (APAP) use in pregnancy and attention deficit/hyperactivity disorder (ADHD) in the offspring.

Approved in 1951, APAP, available in both single-ingredient and combination-ingredient forms, is the most widely-used over-the-counter analgesic and anti-pyretic among adults[5] and children[6] in the U.S. Additionally, findings from two U.S. pregnancy databases indicate 65-70% of pregnant U.S. women report using APAP anytime during pregnancy[1]. Another U.S. study reported 55.8% of women use APAP during the first trimester of pregnancy[7]. Despite APAP's over-the-counter availability and frequent use during pregnancy, little data exists on its safety during pregnancy.

The February 24th issue of *JAMA Pediatrics* featured a study by Liew and colleagues titled "Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders"[2]. This study received significant media attention following its online publication. On March 12 2014, the members of DNRD, Division of Epidemiology-I (DEPI-I), Pediatric and Maternal Health (PMHS), and Office of Communications met to discuss the agency's response to the published study. DNRD asked DEPI to review the study, and a summary and critique of the study follows.

2 REVIEW METHODS AND MATERIALS

This review references the following documents:

- Liew Z, Ritz B, Rebordosa C, Lee P, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr*. 2014; February 24 [Epub ahead of print][2].
- Brandilstuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol*. 2013; 42:1702-1713[4].
- Streissguth AP, Treder RP, Barr HM, Shepard TH, Bleyer WA, Sampson PD, Martin DC. Aspirin and acetaminophen use by pregnant women and subsequent child IQ and attention decrements. *Teratol* 1987; 35:211-219[3].

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

Study investigators used a prospective cohort design among Danish women to assess the association between reported maternal use of APAP and risk of ADHD-like behaviors, hyperkinetic disorders (HKD), and ADHD medication use in the offspring. Women who reported using APAP during pregnancy had a significantly higher risk of having offspring with all three study outcomes. Associations were strongest for women reporting longer durations of prenatal APAP use. A summary of the study design and results is presented in Appendix A.

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3.1.1 Study Objectives

The primary study objective was to evaluate whether APAP use during pregnancy increases the risk of ADHD-like behaviors, HKD diagnosis, or ADHD medication use in the offspring.

3.2 STUDY METHODS

3.2.1 Setting, design, and study population

The authors used data from the Danish National Birth Cohort (DNBC), described as "a nationwide cohort study of pregnancies and children with the aim to study causes of pregnancy complications and diseases in offspring operating in early life, with a special focus on adverse events from medications and infections." The DNBC recruited women who were 6 to 12 weeks of gestation between1996 and 2002, from approximately 50% of all general practitioners in Denmark.

The authors used a prospective cohort design, assessing exposures throughout pregnancy and following the mother and her offspring after birth. The authors used maternal interview data to assess exposure and national administrative data and self-administered questionnaires to assess the outcome(s) of interest.

The study population included 101,041 Dutch-speaking, DNBC-enrolled women. The authors excluded women with non-live birth outcomes (n=6207), non-singleton live births (n=2080), women who emigrated (n=48), women who died (n=3), women with unknown birth outcomes (n=25), and women with missing dates of birth (n=99). Additional exclusions included those women who did not answer all three telephone interviews administered during and after pregnancy (n=28,254). There were two final study cohorts. One cohort consisted of 64,322 mother/child pairs in which the authors assessed HKD diagnoses and ADHD medication use. The second cohort consisted of 40,916 mother/child pairs in which mothers responded to a self-administered online/mail questionnaire when the index child was 7 years of age.

3.2.2 Outcome & Exposure

The primary exposure of interest was self-reported APAP use during pregnancy. Interviews occurred at 6 and 12 weeks gestation and at 6 months postpartum. Using telephone interviews, authors asked women if they had taken any analgesic during pregnancy, and if so, which specific analgesics (either single-ingredient or combination medications) were taken. The authors also asked women about timing and duration of analgesic use during pregnancy. APAP dose/strength was not assessed in this study. The authors classified women as ever-users of APAP throughout the entire pregnancy or users in only the first, second or third trimesters. Women not reporting APAP use any time during pregnancy were considered unexposed (referent).

Study outcomes included reported ADHD-like behaviors, HKD diagnosis, and ADHD medication use. ADHD-like behaviors were reported by the child's mother (or primary caretaker) using the Standardized Strengths and Difficulties Questionnaire (SDQ), administered when the child was 7 years old. The authors asked the mother 25 questions about their child's behavior in the previous 6 months. Scores from four SDQ subscales evaluating emotional symptoms, conduct problems, hyperactivity, and peer problems were summed into a total score, with higher scores indicating more ADHD-like symptoms.

The authors defined HKD based on the presence of primary and secondary diagnosis codes (ICD-10 F90.0-F90.9) from the Danish National Hospital Registry, within Danish Psychiatric Central Registry. The authors note "Since 1995, outpatient and emergency department visits have been

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added to both registries." Only diagnoses made after age 5 were included in the analysis due to "higher diagnostic uncertainty at younger ages."

The investigators identified ADHD medication use in the child if he or she filled two or more prescriptions for methylphenidate (Ritalin), atomoxetine, or modafinil, as indicated in the Danish Prescription Registry.

3.2.3 Covariates

The authors state they included the following potential confounders in the analyses: child's birth year, birthweight, sex, maternal age at birth, parity, gestational age at delivery, socioeconomic status, smoking and alcohol use during pregnancy, pre-pregnancy body mass index, mother's self-reported psychiatric illnesses, muscle and joint diseases, maternal fever during pregnancy, and inflammation and/or infection during pregnancy.

In secondary analyses, the authors stratified on several key confounders, rather than adjust for them in multivariable models. To address potential for confounding by maternal inflammation and infection during pregnancy, the authors stratified results by self-reported episodes of fever, inflammation, or infection during pregnancy. The authors also stratified analyses on maternal psychiatric illness and maternal muscle and joint disease.

3.2.4 Sample Size/Power

The authors do not discuss sample size and power. However, in the population-based study, the authors included all Danish women meeting the inclusion criteria (N=64,322 for HKD and ADHD medication outcomes and N=40,916 for SDQ outcomes).

3.2.5 Statistical Analyses

The authors compared women never exposed to APAP during pregnancy to those ever exposed as well as to exposure in the 1st, 2nd, or 3rd trimester only, both 1st and 2nd trimesters, both 2nd and 3rd trimesters, both 1st and 3rd trimesters, and all three trimesters. Additionally, duration of APAP exposure was assessed by comparing never exposed to those exposed for durations of 1, 2-5, 6-10,11-20, and >20 weeks.

For analyses of HKD diagnoses and ADHD medication use, the authors performed Cox proportional hazards regression to estimate hazards ratios and 95% confidence intervals. Accumulation of person time began on the date of the child's 5th birthday and ended at the first of the following: HKD diagnosis, the date of the first ADHD medication dispensing (assuming the child ultimately had two prescriptions), death, emigration, or end of follow-up (last day of record linkage in 2011).

For analyses of ADHD-like behaviors (using SDQ scores), the authors used "generalized linear models with a log-link function and a Poisson distribution" to estimate rate ratios and 95% CIs. Using a dichotomous variable for SDQ score, they set a cut-point score of 17 to differentiate ADHD-like behaviors from those without these behaviors. The authors note that using a score of 17 or higher would result "in high specificity for ADHD-like behaviors."

The authors specified they performed four sensitivity analyses. First, they analyzed SDQ score as a linear variable rather the dichotomous variable. Second, they restricted analyses to subjects "whose SDQ score was reported by the mother…and not the father or other caregiver." Third, to assess diagnostic differences between hospital types (psychiatric versus general hospital), the authors stratified analyses by hospital type. Finally, the authors stratified by child's sex and

"adjusted for the most commonly used non-steroidal anti-inflammatory drugs among pregnant women…"

3.3 STUDY RESULTS

3.3.1 Descriptive characteristics

Approximately 56% and 55% of mothers reported using APAP during pregnancy in the ADHD-like behaviors cohort and HKD diagnoses and ADHD medications cohort, respectively. Among the ADHD-like behaviors cohort, women reporting APAP use had a slightly higher prevalence of psychiatric illness (20.2% vs 19.1%), fever during pregnancy (33.0% vs 28.2%), muscle and joint disease during pregnancy (12.5% vs 10.5%) , and infection and inflammation during pregnancy (13.3% vs 11.4%), compared to the total cohort (exposed and unexposed).

At the end of follow-up, the authors note the mean age of children was 10.7 years for HKD diagnoses and 11.2 years for ADHD medications. The prevalence of selected characteristics was also greater among women in HKD diagnoses and ADHD medication cohort who reported APAP exposure compared to the total cohort: psychiatric illness (16.7% vs 14.9%), fever during pregnancy (33.4% vs 28.7%), muscle and joint disease during pregnancy (13.3% vs 11.2%), and infection and inflammation during pregnancy (13.2% vs 11.4%).

3.3.2 ADHD-like behaviors

Women who reported APAP use during pregnancy were more likely to report SDQ scores ≥17 in their child when compared to unexposed women (aRR=1.13, 95% CI=1.01-1.27). The authors report no increases to modest increases in risk ratios among exposed women compared to unexposed women for components of the SDQ scale including emotional symptoms (aRR=1.05, 95% CI=0.98-1.13), conduct problems (aRR=1.14, 95% CI=1.05-1.25), hyperactivity (aRR=1.17, 95% CI=1.07-1.28), peer problems (aRR=1.01, 95% CI=0.91-1.11), and prosocial behavior (aRR=1.00, 95% CI=0.88-1.15).

Women exposed only in the first trimester had no increased risk of ADHD-like behaviors in their child compared to unexposed women (aRR=0.97, 95% CI=0.78-1.19) (sponsor's Table 3), while women exposed in both the second and third trimester had a significantly higher risk of ADHD-like behaviors in their child compared to unexposed women (aRR=1.44, 95% CI=1.12-1.87). This increased risk was attenuated, albeit statistically significant, for women exposed in all three trimesters (aRR=1.24, 95% CI=1.03-1.48).

Analyses of duration of APAP use suggest that compared to unexposed women, those exposed for up to one week have no increased risk of ADHD-like symptoms in their child (aRR=0.95, 95% CI=1.14), while women exposed for greater than 20 weeks have a 46% increase in having a child with ADHD-like behaviors (aRR=1.46, 95% CI=1.16-1.85). Risk ratios for women exposed for 2-5 weeks, 6-10 weeks, and 11-20 weeks, compared to unexposed women, were 1.18 (95% CI=1.00-1.40), 1.30 (95% CI=1.00-1.70), and 1.09 (95% CI=0.81-1.47), respectively. The p-value for trend was ≤0.001 (sponsor's Table 3).

3.3.3 HKD diagnoses

Women reporting any APAP use in pregnancy were significantly more likely to have a child with an HKD diagnosis compared to unexposed women (aRR=1.37, 95% CI=1.19-1.59). The magnitude of associations were similar for women exposed in both first and second trimesters (aHR=1.31, 95% CI=0.93-1.85), second and third trimesters (aHR=1.30, 95% CI=0.92-1.84), and first and third trimesters (aHR=1.41, 95% CI=1.08-1.84). The strongest association observed for HKD diagnosis occurred in women exposed in all three trimesters compared to unexposed

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women (aRR=1.61, 95% CI=1.30-2.01). Results for any prenatal APAP use and APAP use in all three trimesters compared to non-use did not appreciably differ when the authors limited analyses to mothers with no psychiatric history, mothers without fever, inflammation and infection during pregnancy, and mothers without muscle and joint disease (sponsor's eTable 2 in Appendix B). Results were similar when stratified on child's sex, albeit hazard ratios were less precise for girls than for boys. The authors observed a significant trend ($p<0.001$) in the association by increasing duration of use. Hazard ratios (95% CIs) for women exposed for up to 1 week, 2-5 weeks, 6-10 weeks, 11-20 weeks, >20 weeks were 1.30 (1.05-1.61), 1.19 (0.95-1.48), 1.65 (1.19-2.28), 1.66 (1.20-2.30), and 1.84 (1.39-2.45), respectively. The sponsor's Table 4 (below) summarizes these findings.

3.3.4 ADHD medication use

Women reporting any APAP exposure during pregnancy were significantly more likely to have a child who used ADHD medication compared to unexposed women (aRR=1.29, 95% CI=1.15-1.44). Hazard ratios (95% CIs) for APAP use in only one trimester were 1.09 (0.89-1.33), 1.20 (0.91-1.55), and 1.28 (1.08-1.52) for use in only the first, second, or third trimester, respectively. Women exposed in all three trimesters had a 44% increase in the risk of having a child taking ADHD medication compared to unexposed women (aRR=1.44, 95% CI=1.21-1.72). Similar to findings for HKD diagnosis, results of any prenatal APAP use and APAP use in all three trimesters compared to non-use did not appreciably differ when the authors limited analyses to mothers with no psychiatric history, mothers without fever, inflammation and infection during pregnancy, and mothers without muscle and joint disease (sponsor's eTable 2 in Appendix B). Results did not differ by child's sex.

The authors report a significant trend in the association between duration of prenatal APAP use and ADHD medication in the child ($p<0.001$). Compared to unexposed women, those taking APAP for up to 1 week had a 18% increase in the risk of having a child take ADHD medications (aHR=1.18, 95% CI=1.00-1.40) while women exposed for >20 weeks had a 53% increase (aHR=1.53, 95% CI=1.21-1.94).

Table 3. Risk Ratios for ADHD-Like Behavioral Problems (Higher SDQ Scores) in Children at Age 7 Years and Maternal Acetaminophen Use (Timing and Weeks) During Pregnancy

Prenatal Exposure and Timing	No.		Risk Ratios	
	Total Difficulties (Scores ≥17)	Noncases	Crude	Adjusted (95% CI)[a]
Acetaminophen use during pregnancy				
Never user	458	17 730	1.00	1 [Reference]
1st trimester only	111	3915	1.09	0.97 (0.78-1.19)
2nd trimester only	59	2031	1.12	1.06 (0.81-1.40)
3rd trimester only	150	4350	1.32	1.04 (0.86-1.25)
Both 1st and 2nd trimesters	48	1601	1.16	1.03 (0.76-1.38)
Both 2nd and 3rd trimesters	68	1477	1.75	1.44 (1.12-1.87)
Both 1st and 3rd trimesters	104	2682	1.48	1.23 (0.99-1.53)
All 3 trimesters	162	3938	1.57	1.24 (1.03-1.48)
Duration of acetaminophen use throughout pregnancy, wk				
0	458	17 730	1.00	1 [Reference]
1	160	5689	1.09	0.95 (0.79-1.14)
2-5	199	5550	1.37	1.18 (1.00-1.40)
6-10	65	1453	1.70	1.30 (1.00-1.70)
11-20	50	1374	1.39	1.09 (0.81-1.47)
>20	87	1714	1.92	1.46 (1.16-1.85)
P value for trend[b]				<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; SDQ, Strengths and Difficulties Questionnaire.

[a] Adjusted maternal age at birth, sex of child, child's birth year, gestational age, birth weight, parity, socioeconomic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal prepregnancy body mass index, parent's behavioral scores in childhood, mother's ever having had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy.

[b] Week of acetaminophen use is modeled as a continuous variable in trend test.

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Table 4. Hazard Ratios for HKD Hospital Diagnosis or ADHD Medication Redemption According to Maternal Acetaminophen Use During Pregnancy

Prenatal Exposure and Timing	Hospital-Diagnosed HKD			ADHD Medication		
	No. of Cases (Person-years)	Hazard Ratios		No. of Cases (Person-years)	Hazard Ratios	
		Crude	Adjusted (95% CI)[a]		Crude	Adjusted (95% CI)[a]
Acetaminophen use during pregnancy						
Never used	283 (159 209)	1.00	1 [Reference]	478 (170 264)	1.00	1 [Reference]
Ever used	551 (204 042)	1.52	1.37 (1.19-1.59)	877 (217 945)	1.43	1.29 (1.15-1.44)
1st trimester only	88 (34 887)	1.42	1.35 (1.07-1.72)	120 (37 288)	1.15	1.09 (0.89-1.33)
2nd trimester only	43 (18 714)	1.29	1.26 (0.91-1.73)	70 (20 011)	1.25	1.20 (0.91-1.55)
3rd trimester only	103 (41 418)	1.40	1.22 (0.97-1.53)	182 (44 262)	1.47	1.28 (1.08-1.52)
Both 1st and 2nd trimesters	37 (14 771)	1.41	1.31 (0.93-1.85)	52 (15 789)	1.17	1.09 (0.81-1.45)
Both 2nd and 3rd trimesters	37 (14 009)	1.49	1.30 (0.92-1.84)	77 (14 936)	1.84	1.63 (1.28-2.07)
Both 1st and 3rd trimesters	70 (25 291)	1.56	1.41 (1.08-1.84)	116 (26 938)	1.53	1.39 (1.13-1.71)
All 3 trimesters	120 (36 463)	1.84	1.61 (1.30-2.01)	181 (38 980)	1.65	1.44 (1.21-1.72)
Duration of acetaminophen use throughout pregnancy, wk						
0	283 (159 209)	1.00	1 [Reference]	478 (170 264)	1.00	1 [Reference]
1	128 (51 493)	1.40	1.30 (1.05-1.61)	197 (55 123)	1.27	1.18 (1.00-1.40)
2-5	115 (49 338)	1.32	1.19 (0.95-1.48)	211 (52 807)	1.43	1.29 (1.10-1.52)
6-10	44 (13 026)	1.90	1.65 (1.19-2.28)	68 (13 984)	1.74	1.49 (1.15-1.93)
11-20	43 (12 348)	1.97	1.66 (1.20-2.30)	55 (13 264)	1.49	1.24 (0.94-1.65)
>20	61 (16 341)	2.07	1.84 (1.39-2.45)	88 (17 431)	1.78	1.53 (1.21-1.94)
P value for trend[b]			<.001			<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HKD, hyperkinetic disorder.

[a] Adjusted maternal age at birth, sex of child, child's birth year, gestational age, birth weight, parity, socioeconomic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal prepregnancy body mass index, mother's ever having had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy.

[b] Week of acetaminophen use is modeled as a continuous variable in trend test.

3.4 Study Discussion and Conclusions

The authors summarize their findings of a consistently increased risk of ADHD-related study outcomes among women taking APAP in pregnancy compared to unexposed women. They note, "associations were stronger for acetaminophen use in more than 1 trimester, and we found exposure response trends with increasing frequency of use during gestation." The authors consider the implications of their results and state that if the observation associations are causal, "acetaminophen should no longer be considered a safe drug for use in pregnancy." They further present a biological mechanism to explain the observed increased associations by suggesting APAP may be an endocrine disruptor capable of disrupting fetal neurodevelopment.

The authors discuss several study strengths. One such strength discussed is the "availability of multiple endpoints" including SDQ score, HKD diagnoses, and ADHD medication use to assess "different levels of ADHD." Another study strength the authors note is minimal loss to follow-up (1.3%) in the ADHD medication and HKD diagnoses cohort, which reduced the likelihood of selection bias. Prospective data collection is another study strength discussed by the authors, noting that this method of data collection captures over-the-counter APAP use not captured in prescription databases. Moreover using a prospective design eliminated the possibility of recall bias since mothers were interviewed about APAP used prior to outcome ascertainment.

The authors discuss the possibility of "flawed recall" of APAP use potentially leading to information bias. However the authors note that any exposure misclassification would likely be non-differential, thus resulting in a lower observed risk estimate than in reality (bias towards the null). The authors acknowledge that they did not assess information on APAP dose or quantity of pills taken. They further acknowledge that 28% of mothers who reported APAP use "were unable to specify the gestational week of use". As a result, the authors assigned the trimester exposure as the interview date. Exclusion of these women from analyses of

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exposure duration "impacted the precision of effect estimation, but results and conclusions did not change."

Regarding confounding, the authors state that adjustment for use of other non-steroidal anti-inflammatory drugs and stratification of results on maternal infection and inflammation did not change the results. Notwithstanding adjustment and stratification on potential measured confounders, the authors state "…the possibility of unmeasured residual confounding by indication for drug use, ADHD-related genetic factors, or coexposures to other medications cannot be dismissed."

The authors conclude that given the frequent prenatal APAP exposure, observed associations from this study "might explain some of the increasing incidence in HKD/ADHD" but caution that further research is needed.

3.5 OTHER STUDIES

DEPI also reviewed two additional studies related to the study by Liew et al[2] that did not directly assess ADHD as a study outcome. Brandlistuen et al[4] evaluated the association between prenatal APAP use among Norwegian women and neurodevelopment status in the offspring using a sibling-controlled cohort study. The sibling-controlled analyses eliminated confounding by familial and genetic factors. Women were asked about APAP and ibuprofen use during pregnancy at 17 and 30 weeks gestation as well as 6 months after delivery. Siblings concordant for APAP exposure (both exposed or both unexposed) were compared to siblings discordant for APAP exposure for use <28 days and ≥28 days. The authors state the 28-day cut-point served to differentiate between short-term and long-term APAP users. The authors also performed a cohort analysis (non-sibling controlled) comparing no exposure to APAP exposure for <28 days and ≥28 days in pregnancy. Using a questionnaire completed by the mother when her children were 3 years of age, the authors assessed maternal responses to questions related to their children's psychomotor development, behavior (internalizing and externalizing), and temperament (emotionality, activity, sociability, and shyness). In the sibling-controlled analysis comparing mean differences in outcome between discordant sibling pairs and concordant pairs, APAP use of <28 days was not associated with behavioral and temperament problems. However, APAP use of ≥28 days was significantly associated with both internalizing and externalizing behaviors (β=0.24, 95% CI=0.12–0.37 and β=0.14, 95% CI=0.01-0.28, respectively). Moreover, APAP use of ≥28 days was also significantly associated with higher activity levels (β=0.22, 95% CI=0.11-0.36). In cohort analyses, compared to unexposed mothers, those reporting APAP use for <28 days and ≥28 days were significantly more likely to have a child with externalizing behaviors (β=0.05, 95% CI=0.03-0.07 and β=0.13, 95% CI=0.07-0.18, respectively). No significant associations were observed between APAP use and internalizing behaviors or increased activity levels. The authors did not observe any interaction between trimester and exposure for any study outcome (P>0.01). In sibling-control analyses, prenatal ibuprofen use was not associated with externalizing behavior or increased activity levels. The authors state they were unable to assess the clinical importance of their findings such as a potential association with ADHD. They further note that associations observed with APAP that were not observed with ibuprofen suggest "a specific effect of paracetamol less likely to be confounded by indication." Unlike the endocrine-disruption hypothesis proposed by Liew et al to explain their findings, Brandlistuen et al speculate that APAP may influence neurodevelopment in the offspring via oxidant/antioxidant imbalance.

Streissguth et al[3] assessed the association between prenatal APAP and aspirin exposure (at up to five months of gestation) and child IQ and attention decrements at age four. The authors assessed child IQ using the Weschler Preschool and Primary Scale of Intelligence instrument. Attention decrement was assessed using a "vigilance paradigm" that required the child to press a button

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when an animal silhouette appeared on a video screen, and errors of omission and commission ("false alarms") were measured for each child . Among a cohort of 425 women, prenatal APAP use was not associated with child IQ score (p<=0.61), errors of omission (p=0.90) or errors of commission (p=0.64). However, the authors report significant associations between prenatal aspirin use and both lower child IQ score and errors of omission.

4 DISCUSSION

Results from Liew et al[2] demonstrate a consistent positive association between reported APAP use in pregnancy and risk of ADHD-related outcomes in the offspring. Effect estimates were generally small for all study outcomes; however APAP exposure is common in pregnancy (>50% of the study population) and hazards ratios were highest among women reporting longer durations of exposure. Results did not appreciably change for analyses stratified on potentially key confounders or effect modifiers.

Residual and unmeasured confounding might explain the observed increased associations. Despite adjustment for a number of potentially confounding variables in each model, biased associations may still exist due to confounding by indication, other medications, genetics, or other factors associated with both APAP exposure and ADHD-related symptoms. The authors did not assess overall markers of health including healthcare utilization and/or medication utilization in the year prior to and during the index pregnancy, which might confound observed associations.

The absence of information on APAP strength and number of pills taken precludes any meaningful interpretation of a dose-response relationship. Stronger associations observed for longer duration of APAP use may reflect effects of timing of exposure (independent of dose), effects of dose/strength, and/or confounding due to the conditions for which the woman took APAP for longer durations or at higher doses.

The prospective study design and exposure ascertainment via maternal interview reduces the potential for selection bias and information bias, respectively. Any misclassification of APAP exposure or study outcome is likely non-differential thus biasing the results towards no positive association (towards safety). Assignment of the interview date in place of the actual exposure date among 28% of women who could not accurately recall the exposure date may have resulted in biased trimester-specific hazards. However exclusion of these women did not change the results and conclusion, and this possible misclassification would not affect analyses of any pregnancy use.

The authors did not assess clinical ADHD diagnoses; however their use of multiple study endpoints from different data sources likely captured a wide range of ADHD severity. The authors' assessment of ADHD-like behaviors, ADHD medication use, and HKD diagnosis attempted represent a broad spectrum of ADHD severity, from mild to severe. A study on predictive validity of clinical diagnostic criteria for ADHD and HKD reported that children with HKD diagnoses had more severe ADHD than other ADHD subtypes[8].

Findings from two additional studies are of unknown clinical significance, but results from one of these studies might strengthen the evidence for an association between prenatal APAP exposure and ADHD risk. Neither Brandlistuen et al[4] nor Streissguth et al[3] assessed ADHD risk in the offspring. However the positive findings reported by Brandlistuen et al for risk of increased activity levels and externalizing behaviors, two behaviors possibly associated with ADHD, might corroborate results observed by Liew et al[2] for ADHD.

5 CONCLUSION

Positive associations observed between prenatal APAP exposure and ADHD in the offspring as reported by Liew et al[2] are noteworthy especially given the frequent use of APAP during pregnancy. However, the study's findings are difficult to interpret due to methodologic limitations and in the context of other existing evidence.

6 RECOMMENDATIONS

DEPI recommends no regulatory action be taken at this time based on available data. However, given the observed safety signal, we recommend DEPI and DNRD stay current on the published safety literature related to APAP use in pregnancy. We further recommend the addition of this safety signal to ongoing agency discussions regarding the safety and regulation of analgesic use during pregnancy.

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8 APPENDICES

Appendix A. Study design summary

	Study
1.1 Objectives/Aims/Scope	To evaluate whether acetaminophen (APAP) use during pregnancy increases the risk of ADHD-like behaviors, ADHD medication use, or HKD diagnosis in the offspring
1.2.1 Design	
1.2.1.1 Type	Population-based, prospective cohort
1.2.1.2 Data Source	Danish National Birth Cohort
1.2.1.3 Time Period	Pregnancies enrolled between 1996 and 2002
1.2.1.4 Criterion (Selection) Standards	Danish-speaking women with live birth outcomes from singleton pregnancies with known birth dates who answered all three telephone interviews administered during and after pregnancy (12 and 30 weeks gestation and 6 months postpartum)
1.2.1.5 Protected Health Information	Written informed consent was obtained from all study subjects. Study approval was also obtained from the Danish data inspectorate and the University of California, Los Angeles institutional review board.
1.2.2 Setting	Denmark, population/registry-based
1.2.3 Exposure/Intervention	APAP exposure during pregnancy
1.2.4 Outcome(s)	ADHD-like behaviors, ADHD medication use, or HKD diagnosis in the offspring
1.2.5 Covariates	Maternal age at birth, sex of child, child's birth year, gestational age, birth weight, parity, socioeconomic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal pre-pregnancy body mass index, parent's behavioral scores in childhood, mother's ever having had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy
1.2.6 Sample Size	Cohort for ADHD-like behaviors using SDQ scale: N=40,916 Cohort for ADHD medication use and HKD diagnosis:

Reference ID: 3507534

	N=64,322
1.2.7 Statistical Analyses	ADHD-like behaviors (using SQD scores), the authors used "generalized linear models with a log-link function and a Poisson distribution" to estimate rate ratios and 95% CIs. Using a dichotomous variable for SQD score, the set a cut-point score of 17 to differentiate ADHD-like behaviors from those without these behaviors HKD diagnoses and ADHD medication use, the authors performed Cox proportional hazards regression to estimate hazards ratios and 95% confidence intervals. Accumulation of person time began on the date of the child's 5th birthday
1.2.8 Study Results (selected)	**ADHD-like behaviors based on SDQ scale score** Ever vs never exposed: aRR=1.13, 95% CI=1.01-1.27 **HKD diagnosis** Ever vs never exposed: aHR=1.37, 95% CI=1.19-1.59 **ADHD medication use** Ever vs never exposed: aHR=1.29, 95% CI=1.15-1.44

Appendix B. Sponsor's eTable 2

eTable 2. Hazard Ratios (HRs) for Hyperkinetic Disorders Hospital Diagnosis or ADHD Medication Redemption According to Maternal Acetaminophen Use During Pregnancy, Stratified by Potential Indications of Acetaminophen Use

	Hospital diagnosed HKD			ADHD Medication		
Use of acetaminophen during pregnancy	No. Cases (Person-years)	Crude HR	Adjusted HR[a] (95% CI)	No. Cases (Person-years)	Crude HR	Adjusted HR[a] (95% CI)
Among mothers that never had psychiatric illnesses						
Never used	229 (139,418)	1.00	1.00 (ref)	384 (149,108)	1.00	1.00 (ref)
Ever used	386 (170,403)	1.38	1.28 (1.08-1.51)	613 (182,123)	1.31	1.21 (1.07-1.38)
In all three trimesters	80 (29,765)	1.63	1.48 (1.14-1.92)	133 (31,806)	1.62	1.47 (1.21-1.80)
Among mothers that did not have fever, inflammation and infections during pregnancy						
Never used	205 (112,679)	1.00	1.00 (ref)	341 (120,562)	1.00	1.00 (ref)
Ever used	334 (120,478)	1.52	1.37 (1.15-1.63)	522 (128,767)	1.43	1.30 (1.13-1.49)
In all three trimesters	68 (21,022)	1.77	1.56 (1.18-2.06)	100 (22,491)	1.57	1.41 (1.12-1.77)
Among mothers that did not have disease in muscles and joints during pregnancy						
Never used	258 (145,024)	1.00	1.00 (ref)	434 (155,144)	1.00	1.00 (ref)
Ever used	430 (175,467)	1.38	1.25 (1.07-1.46)	706 (187,536)	1.35	1.23 (1.09-1.39)
In all three trimesters	84 (29,778)	1.58	1.40 (1.09-1.80)	135 (31,842)	1.51	1.35 (1.11-1.64)

[a] Adjusted maternal age at birth, gender of child, child's birth year, gestational age, birth weight, parity, socio-economic status of mother, maternal smoking and alcohol drinking during pregnancy, maternal pre-pregnancy body mass index, mother's ever had mental health problems, and maternal diseases in muscles/joints, fever, or infection/inflammation during pregnancy.

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